

AMENDMENT TO THE CLAIMS

This listing of claims replaces all prior versions and listings of all claims in the application:

1. (Currently amended) A variant RANKL protein comprising an amino acid modification at C221S and I247E and at ~~at~~ least one further amino acid modification ~~position~~ selected from the group consisting of: ~~H180, K181, H189, D190, R191, G192, S197, R223M, R223E, R223Q, H225A, H225T, H225N, H225E, H225R, E226Q, E226D, E226R, T227, S228, Q237T, Q237K, Q237E, K248, I249, H253, S268, E269R, E269T, E269Q and E269K, F270, R284, S297, D300, and D302~~ as compared to amino acids 68-317 (SEQ ID NO: 1) of full-length wild-type human RANKL.
2. (Currently amended) A variant RANKL protein according to claim 1, wherein said variant RANKL protein further comprises at least one set of substitutions amino acid modifications selected from the group consisting of: a) ~~E269 and F270, b) (H225A, H225T, H225N, H225E, or H225R) and (E269R, E269T, E269Q or E269K), e) H225 and F270, d) R191 and I249, e) G192 and H225, f) H225 and I249, g) H225 and I249, h) E226 and I249, i) T227 and K248, j) S228 and I249, k) D190 and K248, l) D190 and H225, m) G192 and K248, n) (H225A, H225T, H225N, H225E, or H225R), and (E226Q, E226D, E226R) and F270, o) R191, E226 and K248, p) G192, K248 and F270, and q) G192, H225 and I249.~~
3. (Cancelled) A variant RANKL protein according to claim 1, wherein said variant RANKL protein comprises substitutions amino acid modifications at C221S/~~and~~ I247E and at least one further substitution amino acid modification selected from the group consisting of: H180E, K181Q, K181E, H189R, R191Q, R191E, G192A, S197E, R223M, R223E, R223Q, H225T, H225N, H225E, H225R, E226Q, E226D, E226R, T227K, S228E, S228H, Q237T, Q237K, Q237E, K248E, I249Q, H253S, H253T, S268D, E269R, E269T, E269Q, E269K, F270T, F270K, F270E, F270V, R284E, S297Q, D300N, D302H, and D302E.
4. (Currently amended) A variant RANKL protein according to claim 1, wherein said variant RANKL protein comprises substitutions amino acid modifications at C221S/~~and~~ I247E and

at least one further set of amino acid modifications ~~substitutions~~ selected from the group consisting of: a) ~~E269T and F270T~~, b) H225E and E269K, e) ~~H225E and F270T~~, ~~b~~d) H225R and E269K, e) ~~H225R and F270T~~, f) ~~R191E and I249R~~, g) ~~G192A and H225N~~, h) ~~H225N and I249R~~, i) ~~H225R and I249R~~, j) ~~E226R and I249R~~, k) ~~T227Q and K248E~~, l) ~~E226Q and I249R~~, m) ~~T227K and K248E~~, n) ~~S228E and I249R~~, o) ~~D190T and K248E~~, p) ~~D190T and H225R~~, q) ~~D190Q and K248E~~, r) ~~G192A and H225R~~, s) ~~D190Q and H225R~~, t) ~~G192A and K248E~~, u) ~~and c) H225E, and E226D and F270T~~, v) ~~R191K, E226R and K248E~~, w) ~~R191K, E226Q and K248E~~, x) ~~G192A, K248E and F270T~~, y) ~~G192A, H225N and I249R~~, and z) ~~G192A, H225R and I249R~~.

5. (Currently amended) A variant RANKL protein according to claim 1, wherein said variant RANKL protein comprises amino acid modifications ~~at substitutions~~ C221S/ ~~and~~ I247E and at least one further ~~substitution~~ amino acid modification selected from the group consisting of: ~~H180E, K181Q, K181E, R191E, R223M, R223E, R223Q, E226R, T227K, S228E, S228H, Q237K, K248E, I249R, E269T, and E269Q, D302E, H253S, and H253T~~.
6. (Cancelled) A variant RANKL protein according to claim 1, wherein said variant RANKL protein is an antagonist.
7. (Cancelled) A variant RANKL protein according to claim 6, wherein said variant RANKL protein is substantially unable to bind RANK receptor.
8. (Cancelled) A variant RANKL protein according to claim 6, wherein said variant RANKL protein is substantially unable to bind OPG.
9. (Cancelled) A variant RANKL protein according to claim 6, wherein said variant RANKL protein binds to a RANK receptor but does not substantially activate the RANK receptor.
10. (Cancelled) A variant RANKL protein according to claim 9, wherein said variant RANKL protein is substantially unable to bind OPG.
11. (Currently amended) A variant RANKL protein according to claim 1, wherein said variant RANKL protein further comprises at least one amino acid ~~modification~~ ~~at at least one~~

~~position selected from the group consisting of: a) G192, b) R223M, R223E, or R223Q, e) Q237T, Q237K, or Q237E, d) H225A, H225T, H225N, H225E, or H225R, f) E269R, E269T, E269Q or E269K, and g) E226Q, E226D, or E226R, I249, h) K248, and i) F270.~~

12. (Currently amended) A variant RANKL protein according to claim 11, wherein said variant RANKL protein further comprises amino acid modifications at at least one set of positions selected from the group consisting of: (a) (H225A H225T, H225N, H225E, or H225R) and (E269R, E269T, E269Q and E269K); (b) H225 and F270; (c) G192, H225, and I249; and (d) G192, K248, and F270.
13. (Currently amended) A variant RANKL protein according to claim 11, wherein said variant RANKL protein comprises amino acid modifications at substitutions C221S/ and I247E and at least one further amino acid modification substitution selected from the group consisting of: R223M, R223E, R223Q, and Q237K.
14. (Currently amended) A variant RANKL protein according to claim 11, wherein said variant RANKL protein comprises amino acid modifications at substitutions C221S/ and I247E and at least one further set of amino acid modification at substitutions selected from the group consisting of: a) H225R and E269K, b) H225R and F270T, c) G192A, K248E and F270T, d) G192A, H225N and I249R, and e) G192A, H225R and I249R.
15. (Cancelled) A variant RANKL protein according to claim 11, wherein said variant RANKL protein does not substantially bind to OPG.
16. (Currently amended) A variant RANKL protein according to claim 1, wherein said variant RANKL protein further comprises at least one modification at at least one position selected from the group consisting of: R191, G192, H225A H225T, H225N, H225E, H225R, E226Q, E226D, E226R, K248, I249, E269R, E269T, E269Q and E269K, and F270.,
17. (Cancelled) A variant RANKL protein according to claim 16, wherein said variant RANKL protein further comprises at least one set of modifications at at least one set of positions selected from the group consisting of: (a) E269 and F270; (b) H225 and E269; (c) H225 and

F270; (d) G192 and H225; (e) H225 and I249; (f) R191, E226 and K248 (g) G192, H225 and I249.

18. (Cancelled) A variant RANKL protein according to claim 16, wherein said variant RANKL protein does not substantially bind to RANK.

19. (Currently amended) A variant RANKL protein according to claim 16, wherein said variant RANKL protein comprises amino acid modifications at substitutions C221S/ and I247E and at least one further amino acid modification or set of amino acid modifications-substitutions selected from the group consisting of: H225T, H225N, H225E, H225R, E226Q, E269R, E269K, F270K, F270E, E269T and F270T, (H225E and E269K), H225E and F270T, and (H225R and E269K), H225R and F270T, G192A and H225N, H225N and I249R, H225R and I249R, G192A and K248E, R191K and E226R and K248E, R191K and E226Q and K248E, G192A and K248E and F270T, and G192A and H225N and I249R.

20. (Cancelled) A variant RANKL protein according to claim 1, wherein said variant RANKL protein does not substantially activate osteoclastogenesis.

21. (Cancelled) A variant RANKL protein according to claim 20, wherein said variant RANKL protein further comprises at least one amino acid modification at at least one position selected from the group consisting of: K181, D190, R191, G192, R223, H225, E226, T227, S228, Q237, K248, I249, H253, E269, F270, S297, and D302.

22. (Cancelled) A variant RANKL protein according to claim 20, wherein said variant RANKL protein further comprises at least one set of amino acid modifications at at least one set of positions selected from the group consisting of: (a) H225 and E269; (b) H225 and F270; (c) R191 and I249; (d) G192 and H225; (e) H225 and I249; (f) T227 and K248; (g) D190 and H225; (h) H225, E226 and F270; (i) R191, E226, and K248; (j) G192, K248, and F270; and (k) G192, H225 and I249.

23. (Currently amended) A variant RANKL protein according to claim 21, wherein said variant RANKL protein comprises amino acid modifications substitutions C221S/ and I247E

and at least one further amino acid modification substitution selected from the group consisting of: K181Q, K181E, R191Q, R191E, R223M, R223E, H225T, H225N, H225E, H225R, E226Q, E226D, S228E, S228H, Q237K, Q237E, H253S, H253T, E269R, E269T, E269Q, and E269K, F270T, F270K, F270E, F270E, F270E, S297Q, and D302E.

24. (Cancelled) A variant RANKL protein according to claim 24 1, wherein said variant RANKL protein comprises amino acid modifications substitutions C221S/ and I247E and at least one further set of amino acid modifications substitutions selected from the group consisting of: a) H225E and E269K, b) H225E and F270T, c) H225R and E269K, d) R191E and I249R, e) G192A and H225N, f) H225N and I249R, g) H225R and I249R, h) T227Q and K248E, i) G192A and H225R, j) D190Q and H225R, k) G192A and K248E, l) H225E, E226D and F270T, m) R191K, E226R and K248E, n) R191K, E226Q and K248E, o) G192A, K248E and F270T, and p) G192A, H225N and I249R.
25. (Cancelled) A variant RANKL protein according to claim 1, wherein said variant RANKL protein further comprises at least one amino acid modification at at least one position selected from the group consisting of: H180, K181, R223, E226, T227, S228, Q237, and E269, D302, and H253.
26. (Currently amended) A variant RANKL protein according to claim 25 1, wherein said variant RANKL protein comprises substitutions amino acid modifications C221S/ and I247E and at least one further amino acid modification further substitution selected from the group consisting of: H180E, K181Q, K181E, R223M, R223E, R223Q, E226R, T227K, S228E, S228H, Q237K, E269T, and E269Q, H253S, H253T, and D302E.
27. (Cancelled) A variant RANKL protein according to claim 1 wherein said variant RANKL protein further comprises at least one set of amino acid modifications at at least one set of positions selected from the group consisting of: a) R191 and I249 and b) T227 and K248.
28. (Cancelled) A variant RANKL protein according to claim 27, wherein said variant RANKL protein comprises amino acid modifications substitutions C221S/ and I247E and at least one

further set of amino acid modifications substitutions selected from the group consisting of:
a) R191E and I249R and b) T227Q and K248E.

29. (Cancelled) A variant RANKL protein according to claim 1, wherein said variant RANKL protein functions as a competitive inhibitor of wild type RANKL.
30. (Original) A variant RANKL protein according to claim 1, wherein said variant protein is chemically modified.
31. (Withdrawn – currently amended) A variant RANKL protein according to claim 30, wherein said chemical modification is selected from the group consisting of: PEGylation; and glycosylation; ~~and a fusion of said variant protein to another entity~~.
32. (Previously presented) A pharmaceutical composition comprising a variant RANKL protein according to claim 1 and a pharmaceutical carrier.
33. (Withdrawn - original) A method for treating a RANKL-related condition comprising administration of a variant RANKL protein according to claim 1.